



Complete Summary

GUIDELINE TITLE

Major depression in adults in primary care.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Major depression in adults in primary care. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2007 May. 87 p. [239 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Major depression in adults in primary care. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 May. 81 p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [October 25, 2006, Effexor \(venlafaxine HCl\)](#): Published retrospective studies report that venlafaxine overdose may be associated with an increased risk of fatal outcome.
- [May 12, 2006, Paxil \(paroxetine\) and Paxil CR](#): Changes to the Clinical Worsening and Suicide Risk subsection of the WARNINGS section in the prescribing Information related to adult patients, particularly those who are younger adults.
- [December 8, 2005, Paxil \(paroxetine\)](#): Pregnancy category changed from C to D and new data and recommendations added to the WARNINGS section of prescribing information.
- [September 27, 2005, Paxil \(paroxetine\) and Paxil CR](#): Changes to the Pregnancy/PRECAUTIONS section of the Prescribing Information to describe the results of a retrospective epidemiologic study of major congenital malformations in infants born to women taking antidepressants during the first trimester of pregnancy.
- [July 1, 2005, Antidepressants](#): Public Health Advisory issued to update patients and healthcare providers in response to recent scientific publications that report the possibility of increased risk of suicidal behavior in adults treated with antidepressants.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

SCOPE

METHODOLOGY - including Rating Scheme and Cost Analysis

RECOMMENDATIONS

EVIDENCE SUPPORTING THE RECOMMENDATIONS

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

CONTRAINDICATIONS

QUALIFYING STATEMENTS

IMPLEMENTATION OF THE GUIDELINE

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

CATEGORIES

IDENTIFYING INFORMATION AND AVAILABILITY

DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Major depression

Subtypes:

- Atypical major depressive disorder
- Major depression disorder with psychotic features
- Seasonal affective disorder
- Melancholic
- Catatonic
- Postpartum

GUIDELINE CATEGORY

Diagnosis

Evaluation

Management

Treatment

CLINICAL SPECIALTY

Family Practice

Geriatrics

Internal Medicine

Obstetrics and Gynecology

Psychiatry

Psychology

INTENDED USERS

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Physician Assistants
Physicians
Psychologists/Non-physician Behavioral Health Clinicians

GUIDELINE OBJECTIVE(S)

- To increase the accuracy of diagnosis of major depression
- To improve the frequency of assessment of response to treatment in patients with major depression
- To improve the outcomes of treatment for major depression
- To increase the percent of patients with major depression who continue on antidepressants for an adequate length of time
- To increase the assessment for major depression of primary care patients presenting with any additional chronic condition such as diabetes, cardiovascular disease, or chronic pain
- To improve communication between the primary care physician and the mental health care provider (if patient is co-managed)
- To improve the frequency of assessment of patients with major depression for the presence of substance abuse

TARGET POPULATION

All adults greater than 18 years of age

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Detailed clinical interview
2. Use of standardized depression instrument (e.g., Patient Health Questionnaire [PHQ-9], the Beck Depression Inventory, the Hamilton Rating Scale for Depression [HAM-D], the Quality Improvement for Depression Scale [QIDS]-C, and QID-SR).
3. Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision (DSM-IV TR) criteria
4. Consideration of other mood and anxiety disorders or somatoform disorders
5. Assessment of suicide risk
6. Consideration of substance abuse or psychiatric comorbidity (the Cage-AID [AID= Alcohol Illicit Drugs] screen)
7. Consideration of comorbidities, cultural beliefs, and special populations (geriatrics, pregnancy)

Treatment/Management

1. Patient support, including education and exercise
2. Use of collaborative care model

3. Treatment plan
 - Psychotherapy
 - Medications, including selective serotonin re-uptake inhibitors (SSRIs), venlafaxine, duloxetine, mirtazapine, bupropion, secondary amine tricyclics, and monoamine oxidase inhibitors (MAOIs) (See Table 1 in the original guideline document for more information)
 - Herbal/dietary supplements (S-adenosyl-L-methionine [SAM-e])
4. Follow-up including regular contact, medicine maintenance/tapering
5. Re-evaluation for remission
6. Treatment for non-responders
 - Augmentation therapy (including combination of different classes of antidepressants, combination of lithium with antidepressants, and combination of antidepressants with carbamazepine/valproic acid)
 - Hospitalization
 - Bright light therapy
 - Electroconvulsive treatment (ECT)
7. Referral to mental health provider if necessary
8. Maintenance therapy

MAJOR OUTCOMES CONSIDERED

- Prevalence of depression in the general population
- Symptoms of depression, anxiety, and panic disorder
- Risk factors for depression, anxiety, and panic disorder
- Risk for and rate of suicide or suicide attempts
- Rates of remission, recurrence, relapse, and recovery
- Adverse effects of treatment options

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A literature search of clinical trials, meta-analysis, and systematic reviews is performed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of individual research reports is assessed using a hierarchical rating system.

A. Primary Reports of New Data Collection

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

New Guideline Development Process

A new guideline, order set, and protocol is developed by a 6- to 12-member work group that includes physicians, nurses, pharmacists, other healthcare professionals relevant to the topic, along with an Institute for Clinical Systems Improvement (ICSI) staff facilitator. Ordinarily, one of the physicians will be the leader. Most work group members are recruited from ICSI member organizations, but if there is expertise not represented by ICSI members, 1 or 2 members may be recruited from medical groups or hospitals outside of ICSI.

The work group will meet for seven to eight three-hour meetings to develop the guideline. A literature search and review is performed and the work group members, under the coordination of the ICSI staff facilitator, develop the algorithm and write the annotations and footnotes and literature citations.

Once the final draft copy of the guideline is developed, the guideline goes to the ICSI members for critical review.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developers reviewed published cost analyses.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Critical Review Process

Every newly developed guideline or a guideline with significant change is sent to ICSI members for Critical Review. The purpose of critical review is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the guideline. Critical review also provides an opportunity for clinicians in each group to come to consensus on

feedback they wish to give the work group and to consider changes necessary across systems in their organization to implement the guideline.

All member organizations are expected to respond to critical review guidelines. Critical review of guidelines is a criterion for continued membership within the Institute for Clinical Systems Improvement (ICSI).

After the critical review period, the guideline work group reconvenes to review the comments and make changes, as appropriate. The work group prepares a written response to all comments.

Approval

Each guideline, order set, and protocol is approved by the appropriate steering committee. There is one steering committee each for Respiratory, Cardiovascular, OB/GYN, and Preventive Services. The Committee for Evidence-based Practice approves guidelines, order sets, and protocols not associated with a particular category. The steering committees review and approve each guideline based on the following:

- Member comments have been addressed reasonably.
- There is consensus among all ICSI member organizations on the content of the document.
- Within the knowledge of the reviewer, the scientific recommendations within the document are current.
- Either a critical review has been carried out, or to the extent of the knowledge of the reviewer, the changes proposed are sufficiently familiar and sufficiently agreed upon by the users that a new round of critical review is not needed.

Once the guideline, order set, or protocol has been approved, it is posted on the ICSI Web site and released to members for use. Guidelines, order sets, and protocols are reviewed regularly and revised, if warranted.

Revision Process of Existing Guidelines

ICSI scientific documents are revised every 12 to 36 months as indicated by changes in clinical practice and literature. Every 6 months, ICSI checks with the work group to determine if there have been changes in the literature significant enough to cause the document to be revised earlier than scheduled.

Prior to the work group convening to revise the document, ICSI members are asked to review the document and submit comments. During revision, a literature search of clinical trials, meta-analysis, and systematic reviews is performed and reviewed by the work group. The work group will meet for 1-2 three-hour meetings to review the literature, respond to member organization comments, and revise the document as appropriate.

If there are changes or additions to the document that would be unfamiliar or unacceptable to member organizations, it is sent to members to review prior to going to the appropriate steering committee for approval.

Review and Comment Process

ICSI members are asked to review and submit comments for every guideline, order set, and protocol prior to the work group convening to revise the document.

The purpose of the Review and Comment process is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the order set and protocol. Review and Comment also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes needed across systems in their organization to implement the guideline.

All member organizations are encouraged to provide feedback on order sets and protocol, however responding to Review and Comment is not a criterion for continued membership within ICSI.

After the Review and Comment period, the work group reconvenes to review the comments and make changes as appropriate. The work group prepares a written response to all comments.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): For a description of what has changed since the previous version of this guidance, refer to "[Summary of Changes Report -- May - 2007](#)."

The recommendations for the diagnosis and treatment of major depression in adults are presented in the form of an algorithm with 15 components, accompanied by detailed annotations. An algorithm is provided for [Major Depression in Adults in Primary Care](#); clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (A-D, M, R, X) ratings are defined at the end of the "Major Recommendations" field.

Clinical Highlights

- A reasonable way to evaluate whether a system is successfully functioning in its diagnosis, treatment plan, and follow-up of major depression is to consider:
 - How well the diagnosis is documented
 - How well the treatment team engages and educates patients/families
 - How well the ongoing patient contacts are documented
 - How well the outcomes are measured and documented

(Introduction)

- Patients with any chronic condition should be screened for depression, especially those with diabetes, cardiovascular disease, or chronic pain. Presentations for major depression include:
 - Multiple somatic complaints, weight gain/loss, mild dementia
 - Multiple (>5/year) medical visits; problems in more than one organ system, with the absence of physical findings
 - Fatigue
 - Work or relationship dysfunction/changes in interpersonal relationships
 - Sleep disturbances

(Annotations #1, 9)

- Consider using a standardized instrument to document depressive symptoms. Document baseline symptoms and severity to assist in evaluating future progress, including response and remission rates. (Annotation #2)
- Antidepressant medications and/or referral for psychotherapy are recommended as treatment for major depression without coexisting medical conditions, substance abuse or other specific psychiatric comorbidities. Physical activity and tailored patient education are also useful tools in easing symptoms of major depression. (Annotation #11)
- When antidepressant therapy is prescribed, medication adherence and completion is critical. The patient should be advised of the following:
 - Most people need to be on medication at least 6 to 12 months after adequate response to symptoms.
 - Patients may show improvement at two weeks but need a longer length of time to really see response and remission.
 - Take the medication as prescribed, even after starting to feel better.
 - Do not stop taking the medication without calling the provider. Side effects can be managed by changes in the dosage or dosage schedule.

(Annotation #11)

- If the primary care provider is seeing incremental improvement, continue working with that patient to augment or increase medication dosage to reach remission. This can take up to three months. Don't give up on the patient whether treating in primary care or referring. (Annotation #11, 12)
- The key objectives of treatment are:
 - To achieve remission of symptoms in the acute treatment phase for major depression
 - To reduce patient relapse and reduction of symptoms
 - To return to previous level of occupational and psychosocial function

(Annotation #13)

[Major Depression in Adults in Primary Care Algorithm Annotations](#)

1. Suspect Major Depression

Key Points:

- The major depression syndrome is a disorder of mood involving disturbances in emotional, cognitive, behavioral, and somatic regulation.
- Some clinicians find self-administered instruments (e.g., the Patient Health Questionnaire [PHQ-9] and the Hamilton Rating Scale for Depression [HAM-D]) useful adjuncts to the clinical interview.
- Major depression is a treatable cause of pain, suffering, disability and death, yet primary care providers detect major depression in only 1/3 to 1/2 of their patients with major depression.

A. Presentations for major depression include:

- Multiple (more than 5/year) medical visits
- Multiple unexplained symptoms
- Work or relationship dysfunction
- Changes in interpersonal relationships
- Dampened affect
- Poor behavioral follow-through with activities of daily living or prior treatment recommendations
- Weight gain or loss
- Sleep disturbance
- Fatigue
- Dementia
- Irritable bowel syndrome
- Volunteered complaints of stress or mood disturbance

See also Annotation #9, "Additional Considerations?"

Evidence supporting this recommendation is of classes: B, C, D, R

B. Risk Factors for major depression include:

- Family or personal history of major depression and/or substance abuse
- Recent loss
- Chronic medical illness
- Dysthymia
- Stressful life events that include loss (death of a loved one, divorce)
- Domestic abuse/violence
- Traumatic events (car accident)
- Major life changes (job change)
- Emotional and behavioral reactions to these social stressors can include symptoms of major depression.

One previous episode of major depression is associated with a 50% chance of a subsequent episode, two episodes with a 70% chance, and three or more episodes with a 90% chance. For women, severe obesity (body mass index greater than 40) has been strongly associated with depression. Major depression is also seen in elderly patients with comorbid illnesses, such as cerebrovascular accident (CVA), cancer, dementia or disabilities.

Most studies indicate that in 40% to 60% of patients, a major life event precedes the first episode of major depression.

Patients with a history of mood disorders are at increased risk for postpartum depression. Several depressive conditions may follow childbirth. "Postpartum blues" affects 50% to 85% of mothers in the first two weeks after delivery. It is characterized by mood lability, tearfulness, anxiety and sleep disturbance but usually does not result in functional impairment. No specific treatment is required. If the patient remains significantly depressed three to four weeks following delivery, it should be considered serious and treated, including eliminating medical causes of depressive symptoms such as postpartum thyroid disorders or anemia. The first two to three months postpartum is the period of greatest risk for the development of major depression.

The close relationship of mind and body results in the presentation of medical illness with major depression in various forms:

- Medical illness may be a biological cause (e.g., thyroid disorder, stroke).
- Medical illness or patient's perception of his or her clinical condition and health-related quality of life may trigger a psychological reaction to prognosis, pain or disability (e.g., in a patient with cancer).
- Medical illness may exist coincidentally in a patient with primary mood or anxiety disorder.

See also Annotation #9, "Additional Considerations?"

Evidence supporting this recommendation is of classes: D, R

2. Diagnose and Characterize Major Depression with Clinical Interview

Key Points:

- The U.S. Preventive Services Task Force (USPSTF) recommends screening adults for major depression in clinical practices that have systems in place to assure accurate diagnosis, effective treatment, and follow-up. The purpose of this guideline is to assist ICSI members to develop systems that support effective diagnosis and treatment of major depression.
 - If depression is suspected on the basis of risk factors or common presentations, consider using a standardized instrument to document depressive symptoms.
 - Clinicians should choose the method that best fits their personal preference, the patient population served and the practice setting.
- A. Depressed mood or anhedonia (diminished interest or pleasure in activities) is necessary to diagnose major depression. If depression is suspected on the basis of risk factors or common presentations, consider using a standardized instrument to document depressive symptoms. More importantly, document baseline symptoms and severity to assist in evaluating future progress. Asking the two-

question screen about mood and anhedonia may be as effective as using longer questionnaires:

Over the past two months, have you been bothered by:

- Little interest or pleasure in doing things?
- Feeling down, depressed and hopeless?

If the patient answers "yes" to either one of the above questions, consider using a quantitative questionnaire to further assess whether the patient has sufficient symptoms to warrant a diagnosis of clinical major depression and a full clinical interview.

The use of a mnemonic may likewise be helpful for remembering the symptoms of major depression and dysthymia. SIGECAPS or SIG + Energy + CAPSules is easily remembered and can be used in the clinical interview. It was developed by Dr. Carey Gross of Massachusetts General Hospital and stands for:

Sleep disorder (increased or decreased)
Interest deficit (anhedonia)
Guilt (worthlessness, hopelessness, regret)
Energy deficit
Concentration deficit
Appetite disorder (increased or decreased)
Psychomotor retardation or agitation
Suicidality

Some clinicians find that either self administered or professionally administered instruments are useful adjuncts to the clinical interview. Some examples that are recognized and validated are PHQ-9, the Beck Depression Inventory (BECK), HAM-D, the Quality Improvement for Depression Scale (QIDS)-C, and QID-SR. Regardless, it is crucial to document that the patient meets at least five symptoms for at least two weeks as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV TR) criteria for major depression. One of the symptoms must be depressed mood or loss of interest or pleasure. See Appendices B, C, and D in the original guideline document for example questionnaires.

The nine-item Patient Health Questionnaire (PHQ-9) has been validated for measuring depression severity, as well as for telephonic administration.

Clinicians should choose the method that best fits their personal preference, the patient population served, and the practice setting.

The primary objective is to use a standardized instrument that will quantify and document future progress, including response and remission rates.

Evidence supporting this recommendation is of classes: C, D, R

B. Determine history of present illness including:

- Onset may be gradual over months or years or may be abrupt.
- Severity of symptoms and degree of functional impairment:

People diagnosed with major depression have a heterogeneous course from self-limiting to life-threatening. Predictors of poor outcome include higher severity at initial assessment, lack of reduction of social difficulties at follow-up and low educational level. Categorize severity of symptoms and degree of functional impairment as follows:

Mild: few, if any, symptoms in excess of those required to make the diagnosis and only minor impairment in occupational and/or social functioning

Moderate: symptoms or functional impairment between mild and severe

Severe: several symptoms in excess of those necessary to make the diagnosis and marked interference with occupational and/or social functioning

- Number and severity of previous episodes, treatment responses and suicide attempts.
- Ask about concurrent psychiatric conditions. Obtaining a past psychiatric history is important in terms of understanding prognosis and risk factors. For example, knowledge of past episodes of major depression, past co-occurring mental/behavioral health conditions, and past self-harm attempts is important for establishing risk and need to involve other mental health professionals.
- Psychosocial stressors (significant loss, conflict, financial difficulties, life change, abuse).

C. A past medical history and brief review of systems is generally sufficient to rule out medical disorders causing major depression. Pertinent medical history that may complicate pharmacological treatments include, for example, prostatism, cardiac conduction abnormalities, and impaired hepatic function.

Perform a focused physical examination and laboratory testing as indicated by the review of systems. The benefit of screening laboratory tests, including thyroid tests, to evaluate major depression has not been established.

Reliance on laboratory tests should be greater if:

- The medical review of systems detects symptoms that are rarely encountered in mood or anxiety disorders.

- The patient is older.
- The first major depressive episode occurs after the age of 40.
- The depression does not respond fully to routine treatment.

D. Determine past history of substance abuse/dependence.

- Medications such as steroids, alpha-methyldopa, and hormonal therapy may be associated with major depression.
- Withdrawal from reserpine and propranolol may be associated with major depression.
- Use of alcohol and hypnotics might be mimicking depression but comorbidity is common.
- Withdrawal from cocaine, anxiolytics, and amphetamines may be mimicking depression.
- Idiosyncratic reactions to other medications can occur and if possible, a medication should be stopped or changed if depression develops after beginning its use. If symptoms persist after stopping or changing medication, reevaluate for a primary mood or anxiety disorder.

3. Five or More Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision (DSM-IV TR) Criteria Present?

- A. Five or more of the following symptoms have been present and documented during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-congruent delusions or hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

- B. The symptoms do not meet criteria for a mixed episode.
- C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
- E. The symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one), the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

The assessment of major depressive disorders should include the DSM-IV TR numerical rating of the disorder with all 5 digits, thus including a severity rating. For example, 296.22 (Major depressive disorder, single episode, moderate severity).

4. Consider Other Mood and Anxiety Disorders or Somatoform Disorders

Patients with some depressive symptoms who do not meet full DSM-IV TR criteria for major depression often respond positively to antidepressant medication and/or psychotherapy. Emerging evidence also supports the use of bright light therapy in some of the cases of milder depression.

Presentations particularly suggestive of an anxiety disorder include:

- Medically unexplained symptoms of autonomic excitation such as:
 - Cardiac (chest pain, atypical chest pain, palpitations, shortness of breath, hyperventilation)
 - Gastrointestinal (epigastric distress, irritable bowel syndrome)
 - Neurologic (headache, dizziness, paresthesias)
 - Panic attacks
- Emergency room visit for medically unexplained somatic symptoms, particularly chest pain

These symptoms can cause significant impairment, suffering, and disability. Antidepressants should be considered, though the evidence for their efficacy is less well established with these disorders than with major depression. Other depression categories include dysthymic disorder and depressive disorder NOS (not otherwise specified.) See Appendix A in the original guideline document.

Evidence supporting this recommendation is of classes: A, M

5. Is Patient Unsafe to Self or Others?

Key Points:

- Although there are no good predictors of suicide in specific cases, a number of factors point to heightened risk.

- Ongoing case management enhances positive outcomes for depression.

Assessing suicidal tendencies is a critical but often difficult process with a depressed patient. Consider asking and documenting the following progression of questions:

1. Do you feel that life is worth living?
2. Do you wish you were dead?
3. Have you thought about ending your life?
4. If yes, have you gone so far as to think about how you would do so?
5. Do you have access to a way to carry out your plan?
6. What keeps you from harming yourself?

Many patients will not answer #4 directly or will add "But I'd never do it." Give them positive feedback (e.g., "I'm glad to hear that") but do not drop the subject until she/he has told you the specific methods considered (e.g., gun, medication overdose, motor vehicle accident).

Although there are no good predictors of suicide in specific cases, a number of factors point to heightened risk:

- There are four male suicide completions for every female completion.
- Elderly Caucasian and Asian men over the age of 65 years and Asian women over 80 years are at disproportionate risk.
- Two thirds of elderly suicide completers are in relatively good health. White men over the age of 85 years have six times the risk of suicide completion as the general population. The majority of elderly suicides appear associated with late onset, single episode of depression, and not current poor health. Twenty percent of elderly suicide completers were seen by their physicians within 24 hours of death, 35% within the week, and 75% within the month.
- Substance abuse is a contributing factor in approximately half of suicide completions, although the involvement of intoxication as a risk factor decreases in the elderly.
- The presence of firearms in the home is believed to greatly increase the danger if other risk factors are present. Males in general tend to choose highly lethal means, such as firearms, which greatly increases the risk of death.
- Across all age groups, one in seven suicide completers had contact with their doctor within a week of death.
- When a patient has high levels of all of the following, risk is very high and hospitalization may be needed immediately:
 - Internal emotional pain (e.g., feelings of shame, guilt, humiliation)
 - External stress (e.g., loss of spouse, job, legal troubles)
 - Hopelessness

If any one factor can be substantially alleviated, risk is thought to drop sharply.

Suicide remains a rare occurrence relative to the frequency of depression in the general population; between one and five suicides occur per one thousand patient years of follow-up.

Emerging literature suggests that a past history of self harm attempts, in combination with a history of well developed suicide plans, place the patient at a greater eventual risk of completing a suicide attempt. Circumstances such as clear past examples of a sense of competence to execute an attempt, a sense of courage to make the attempt, behaviors that ensure the availability of means and opportunity to complete, concrete preparations to enact the suicide plan, and a current episode of severe depression combine to pose a greater danger of eventual completed suicide. The clinician should consider previous history of suicide attempts; chemical dependency, personality disorder and/or physical illness; family history of suicide; single status; recent loss by death, divorce or separation; insomnia; panic attacks and/or severe psychic anxiety; diminished concentration; anhedonia; hopelessness; or suicidal ideation.

Evidence supporting this recommendation is of classes: A, C, M, R

7. Assess Need for Additional Resources: Substance Abuse or Psychiatric Comorbidity, Especially Bipolar Disorder?

Key Points:

- The medical literature does not support definitive statements about the best way(s) to treat patients who are diagnosed with both major depression and substance abuse/dependence.
- Some patients presenting with a major depressive episode have a bipolar disorder, for which effective treatment may differ significantly from other depressed patients.

Major depression may be associated with other psychiatric problems including personality disorders, anxiety disorders, obsessive-compulsive disorders, eating disorders, and substance abuse.

The medical literature does not support definitive statements about the best way(s) to treat patients who are diagnosed with both major depression and chemical abuse/dependence. The majority of studies reviewed indicate that success in treating dependency on alcohol, cocaine, and other abused substances is more likely if accompanying depression is addressed. Fewer investigators have looked at whether treating substance abuse is helpful in reducing depression. There is some evidence that patients with major depression that is secondary to their substance abuse may have remission of their depressed mood once the substance abuse is treated. However, it is difficult to separate secondary depression from primary depression that predates or is separate from the substance use.

Studies to assess the efficacy of concurrent treatment of major depression and substance abuse are limited in number and of variable quality. Although results are not fully consistent, the preponderance of available evidence suggests that pharmacotherapy can be of benefit in treating both substance

abuse and depression in patients who have both disorders. Agents studied include amantadine (a dopamine agonist), desipramine (a tricyclic antidepressant), and fluoxetine (a selective serotonin reuptake inhibitor [SSRI]).

The algorithm reflects the uncertainty in this area. At diamond #7 it splits into two possible paths. If yes -- a depressed patient is felt to be chemically dependent and treatment of the substance abuse should be considered, either before or while treating the depression. However, if no -- a depressed patient refuses treatment for substance abuse, has a medical comorbidity, or is of a special population, it is appropriate to focus primarily on the depression keeping the special circumstances in mind. It is reasonable to attempt to treat the depression while continuing to assist the patient to work toward efforts to understand their special needs.

Evaluation and treatment for chemical dependency is beyond the scope of this guideline. A referral may be appropriate.

Evidence supporting this recommendation is of classes: A, B, C, D, R

The CAGE(AID) Screen

Current alcohol or other drug problems can be screened by asking a few questions that can be easily integrated into a clinical interview. A common screen is the CAGE screen.

The CAGE or CAGE(AID) should be preceded by two questions:

1. Do you drink alcohol?
2. Have you experimented with drugs?

If the patient has experimented with drugs, ask the CAGE(AID) questions. CAGE(AID) questions are modified with italicized text.

CAGE(AID) Screen
Have you ever:
C felt you ought to cut down on your drinking (or drug use)?
A had people annoy you by criticizing your drinking (or drug use)?
G felt bad or guilty about your drinking (or drug use)?
E had a drink (or drug use) as an eye opener first thing in the morning to steady your nerves or get rid of a hangover or to get the day started?
If substance abuse is present or suspected, consider referral for substance abuse assessment.

Each affirmative response earns one point. One point indicates a possible problem. Two points indicate a probable problem.

The CAGE screen is short in length and easy to administer, however other screening tools may also be useful. It is important to screen for substance abuse using a validated tool, and which tool to use depends on the provider/system's preferences and needs.

Refer to the original guideline document for examples of substance abuse screening tools.

Bipolar Disorder

Some patients presenting with a major depressive episode have a bipolar disorder, for which effective treatment may differ significantly from other depressed patients. When assessing a patient, consider asking about manic or hypomanic episodes.

- Has there been a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least four days (hypomanic episode) or at least one week (manic episode)?
- During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
 1. Inflated self-esteem or grandiosity
 2. Decreased need for sleep
 3. More talkative than usual or pressure to keep talking
 4. Flight of ideas or subjective experience that thoughts are racing
 5. Distractibility
 6. Increase in goal-directed activity or psychomotor agitation
 7. Excessive involvement in pleasurable activities that have a high potential for painful consequences

An example of an assessment tool is the Mood Disorder Questionnaire.

If these criteria are met, the patient may have a bipolar mood disorder. Treatment for this falls out of the scope of this guideline.

Ask patients with major depression about a history of manic or hypomanic symptoms (abnormally elevated, expansive or irritable mood). Patients with a history of manic (bipolar) symptoms now presenting with major depression may be destabilized if treated only with antidepressant drugs. Behavioral health involvement is advised with these patients absent a prior history of successful primary care management.

Be aware of ongoing mental illness diagnosis or other mental health illnesses and comorbidities.

Evidence supporting this recommendation is of class: C

8. Involve Behavioral/Chemical Health

Consider involving same day behavioral health for:

- Suicidal thoughts and/or plans which make the clinician uncertain of the patient's safety
- Assaultive or homicidal thoughts and/or plans which make the clinician uncertain about the safety of the patient or others
- Recent loss of touch with reality (psychosis)
- Inability to care for self/family

Involvement could include:

- Appointment with psychiatrist and/or psychotherapist
- Phone consultation with psychiatrist and/or psychotherapist
- Referral to the emergency department

Evidence supporting this recommendation is of classes: A, C, D, M, R

9. Additional Considerations?

Medical Comorbidities

Be aware of the increased incidence of depression in chronic comorbid conditions such as chronic pain, diabetes, cancer, Parkinson's disease, and cardiovascular disease. Depression may increase in frequency with acute conditions such as fractured leg, back pain with disability, acute myocardial infarction (MI), stroke, etc. Difficulties coping with a medical condition may also play a role.

The following conditions are particularly important for screening, given the findings.

Cardiovascular Disease

Some studies have shown that major depression is associated with an increased risk of developing coronary artery disease, and has also been shown to increase the risk of mortality in patients after myocardial infarction by as much as fourfold. More recent analyses have disputed this. Moderate to severe depression before coronary artery bypass graft (CABG) surgery and/or persistent depression after surgery increases the risk of death after CABG more than two-fold compared to non-depressed patients.

As yet there are no data to support the hypothesis that antidepressant treatment improves cardiac morbidity and mortality. Nevertheless, consensus opinion is to treat depressed cardiac patients with a safe drug rather than watchful waiting since they would benefit from symptomatic relief of their depressive symptoms and there is a potential improvement in their cardiovascular risk profile.

Although tricyclic antidepressants are effective against depression, they are associated with cardiovascular side effects including orthostatic hypotension, slowed cardiac conduction, antiarrhythmic activity, and increased heart rate.

Selective serotonin reuptake inhibitors (SSRIs) by contrast are well tolerated and have a more benign cardiovascular profile and would be preferred initial agents for treatment of depression in individuals with cardiovascular disease.

Evidence supporting this recommendation is of classes: A, D, M, R

Diabetes

Major depression is associated with an increased number of known cardiac risk factors in patients with diabetes and a higher incidence of coronary heart disease; therefore, screening and treatment of depression in this patient group should be emphasized.

Individuals with diabetes have two-fold higher odds of depression than those without diabetes. High levels of symptoms associated with diabetes that do not correlate with physical or laboratory assessments should prompt the physician to assess for depression.

Depression earlier in life increases the risk of developing diabetes by two-fold.

Depressive symptom severity is associated with poorer diet, medication compliance, and self-care plus functional impairment and higher health care costs.

Evidence supporting this recommendation is of class: D

Chronic Pain

Depression and pain symptoms commonly coexist, exacerbate or attenuate one another, and appear to share biological pathways and neurotransmitters.

Key Clinical Practice Recommendations:

- In those patients presenting with either pain or depressive symptoms, assess both domains. Depression may be more than a facet of chronic pain when significant depression symptoms are present. If comorbidity is found between chronic pain and mild to moderate major depression, treat both conditions for optimal outcomes. If comorbid severe major depressive disorder is diagnosed concurrently with chronic pain, depressive symptoms should be the primary focus of treatment.
- Given that depression and pain symptoms appear to follow the same descending pathways of the central nervous system involving a functional deficiency of the neurotransmitters serotonin, norepinephrine, and dopamine, antidepressant medication is warranted, especially the dual-action tricyclic antidepressants such as amitriptyline or dual action atypical antidepressant reuptake inhibitors such as venlafaxine or duloxetine. Duloxetine is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy. Duloxetine dosed orally at 60 mg once or twice daily, improved mean pain scores from baseline and increased the proportion of patients with at least 50% reduction in pain scores from baseline.

- Combining pharmacologic treatment and cognitive-behavioral therapy appears to produce the most favorable treatment outcomes.

Evidence supporting this recommendation is of classes: A, B, D, M, R

Cultural Beliefs

The concept of depression varies across cultures. In many cultures, for depression to become a problem for which a person seeks medical treatment, symptoms may include psychosis, conversion disorders, or significant physical ailments.

- A person's past cultural and personal experiences influence his/her beliefs and therefore attitudes and preferences. If these experiences are taken into consideration, openness to and readiness to change (including readiness to seek treatment and adhere to treatment) will be enhanced. People of differing racial/ethnic groups are successfully treated using currently available evidence-based interventions when differential personal elements, from biological to environmental to cultural, are considered during the treatment planning process.
- Be aware that psychosocial stressors may be more prevalent with certain populations and the health care team may want to take these issues into consideration as a treatment plan is made. Examples of possible stressors include:
 - Housing
 - Daycare
 - Employment
 - Financial stability
 - Food
 - Transportation
 - Immigration status
- Assess for other resources the client may have used such as elders, native or spiritual advisors/healers, or whoever is within their frame of reference. Acknowledge their role and collaborate if possible/appropriate.
- Many assessment tools may not be useful for certain populations. Screening instruments are validated in certain groups. Use caution when using because a tool may not be applicable to all groups.
- Cost implications for patients often affect adherence, including insurance coverage or generic versus brand name medications. Adherence factors are important for providers to discuss with the patient.
- Symptoms of depression may be perceived differently by various cultures. This may lead to under-recognition or misidentification of psychological distress. In some cultures mood, affect and anxiety symptoms are considered social, moral, or spiritual problems.
- The most common somatic symptoms of depression and anxiety are musculoskeletal pain and fatigue. A provider might consider starting the conversation with the patient on physical symptoms since this is a common presentation of depression in some cultures.

- 10% to 75% of patients are noncompliant with medication use, and rates are higher in intercultural settings because of cultural expectations and communication problems.
- Most empirically supported therapies have been evaluated with white, middle class, English-speaking populations.
- Recent research on depression in low-income minority women in the United States documents significant improvement of symptoms and social functioning regardless of whether treatment was medication or psychotherapy when treatment was sufficiently accessible (availability of child care and transportation).
- Health care providers can create a more comfortable environment for a patient of another culture by acknowledging the impact of culture and cultural differences on physical and mental health.
- A discrepancy between aspiration and achievement may be a better predictor of psychiatric illness than socioeconomic status. The larger the discrepancy between aspiration and achievement, the greater risk of emotional disturbance.

Evidence supporting this recommendation is of classes: C, D, R

Special Populations

Geriatrics

Depression in the elderly is widespread, often undiagnosed and usually untreated. It is a common misperception that it is a part of normal aging. Losses, social isolation and chronic medical problems that older patients experience can contribute to depression.

The rate of depression in adults older than 65 years of age ranges from 7% to 36% in medical outpatient clinics and increases to 40% in the hospitalized elderly. Comorbidities are more common in the elderly. The highest rates of depression are found in those with strokes (30% to 60%), coronary artery disease (up to 44%), cancer (up to 40%), Parkinson's disease (40%), and Alzheimer's disease (20% to 40%). The recurrence rate is also extremely high at 40%.

Similar to other groups, the elderly with depression are more likely than younger patients to underreport depressive symptoms. They often present with nonspecific complaints, such as insomnia, appetite disturbances, lack of energy, fatigue, chronic pain, constipation, and musculoskeletal disorders. For elderly patients, one assessment tool is the Geriatric Depression Scale. See Appendix D in the original guideline document. Clinicians may find it easier to use than other tools because the questions ask for yes/no answers.

The outlook for recovery for the elderly is similar to that for the young when appropriately treated. However, treatment usually has to be continued for longer periods than for the young, since it may take longer to reach remission.

Pharmacotherapy, psychotherapy and electroconvulsive therapy are appropriate modalities to treat depression in the elderly. When using

pharmacotherapy, the physician must carefully consider how the metabolism of the drug may be affected by physiologic changes in the elderly, their comorbid illnesses and the medications used for them. In those individuals who don't respond to the different antidepressants alone, augmentation therapies may be appropriate. This would include psychostimulants, such as cytomel or methylphenidate, or the addition of lithium. Psychotherapy is also appropriate, limited only by cognitive impairments. Electroconvulsive treatment (ECT) may be the most effective and rapid treatment in this situation.

Recurrent depression is common in the elderly. Maintenance therapy with an SSRI (paroxetine in this study) for two years was shown to be effective in preventing recurrent depression after a first time major depression in the elderly over seventy years of age. Interpersonal psychotherapy alone was ineffective.

Evidence supporting this recommendation is of classes: A, M, R

Pregnancy

Depression poses risk for pregnancy. Maternal depression and other stress states have been associated with lower birth weight and gestational age of infant offspring, delivery by cesarean section, and admittance to neonatal care units. Other potential consequences of depression during pregnancy include: poor maternal weight gain or frank weight loss and malnutrition (puts infants at risk for low birth weight), long-term hospitalization, marital discord and divorce, poor prenatal care compliance, difficulty caring for other children, loss of employment, increased harmful behaviors such as nicotine, alcohol, or drug use, and suicide. The challenge is to minimize unnecessary medication exposure to the developing fetus while maintaining the health of the mother. Studies are sparse, specifically regarding the efficacy of psychotherapy and psychotropic treatments. Medication should be used when the risk to the mother and fetus from depression outweighs risks of pharmacotherapy. Maternal illness severity is an important factor in the risk benefit decision-making process. Mild to moderate depressive symptoms may respond to interpersonal psychotherapy which has been modified for pregnancy. More severe depression requires psychopharmacological interventions. It is very possible that antidepressant treatment for depression during pregnancy could reduce or avert some of the potential adverse effects of depression on the mother and her developing fetus. Safety of antidepressants during pregnancy has not been clearly established.

For further information on medications during pregnancy, see the "Medications" section in Annotation #11, "Treatment Plan."

Consideration should be used for bright light therapy as an option for depressed pregnant women. See Annotation #14, "Consider Other Strategies," in the original guideline document for further information on this subject.

10. Address Secondary Causes and/or Adapt a Plan for the Special Population

People with secondary causes for major depression may also have an underlying primary mood or anxiety disorder. Understanding and addressing nuances of special populations may enhance treatment outcomes.

11. Treatment Plan

Key Points:

- Collaborative care is a model for primary care depression treatment that is based on a team performing roles and functions in an organized, collaborative approach.
- Patient information should include diagnosis, prognosis, and treatment options including costs, duration, side effects, and expected benefits.
- Successful programs for the treatment of depression include organized treatment protocols, structured follow-up protocols, systematic monitoring of treatment adherence and effectiveness.
- When considering treatment options, the primary goal is to achieve remission.

Collaborative Care

Studies supporting use of the Collaborative Care Model in which primary care treatment of depression is provided by a team (depression care manager, primary physician, consulting psychiatrist, others) demonstrate improvement in treatment adherence, patient quality of life, and depression outcomes.

The redesign to a team-based collaborative care approach involves:

- Primary care providers using evidence-based approaches to depression care and a standard tool for measuring severity, response to treatment plan and remission
- A systematic way of tracking and reminding patients at appropriate intervals of visits with their primary care physician and monitoring of treatment adherence and effectiveness;
- A team member (care manager role) to utilize the tracking system and make frequent contacts with the patients to provide further education, self-management support, and monitor for response in order to aid in facilitating treatment changes and in relapse prevention; and
- Communication between primary care team and psychiatry to consult frequently and regularly regarding patient under clinical supervision, as well as direct patient visits as needed.

Evidence supporting this recommendation is of classes: A, M, R

See the Key Implementation Recommendations in the "Description of Implementation Strategy" field and Knowledge Resources section in the original guideline document for suggestions and information on implementing the Collaborative Care Model.

Educate and Engage Patient

Successful care of major depression as an illness requires active engagement of each patient and his/her family and ongoing patient education, beginning at the time of diagnosis.

Often, the depressed patient's pessimism, low motivation, low energy, and sense of social isolation and guilt may lead to nonadherence with treatment.

Patient information should include diagnosis, prognosis, and treatment options including costs, duration, side effects, and expected benefits. Emphasize the following six points:

- Depression is a medical illness, not a character defect.
- Recovery is the rule, not the exception.
- Treatment is effective for nearly all patients.
- The aim of treatment is complete remission, not just getting better but staying well.
- The risk of recurrence is significant: 50% after one episode, 70% after two episodes, 90% after three episodes.
- Patient and family should be alert to early signs and symptoms of recurrence and seek treatment early if depression returns.

Patient Self-Management

It is important for the patient to consider and adopt some self-care responsibilities, which may range from simply demonstrating reliable behavior in taking medications and calling the provider with side effects to agreeing to participate in sessions, journaling and completing homework, which is necessary for some cognitive behavioral therapies. Written materials are helpful to reinforce information shared during the discussion. Patients who commit to some self-care responsibilities and receive this education compared with those who do not are more likely to continue treatment, rather than prematurely abandon it, and are more likely to attain better outcomes.

Education topics should include:

- The cause, symptoms and natural history of major depression
- Treatment options and the process of finding the best fit for a given individual
- Information on what to expect during the course of treatment
- How to monitor symptoms and side effects
- Follow-up protocol (office visits and/or telephone contacts)
- Early warning signs of relapse or recurrence
- Length of treatment
- Communication with the caregiver. A patient should plan to make appointments for six months to one year. Frequency of visits will depend on depression severity. See "Establish Follow-Up Plan" further in this annotation.

Exercise

Evidence suggests that physical activity at a dose consistent with public health recommendations is a useful tool for easing major depression symptoms. Among individuals with major depression, exercise therapy is feasible and is associated with significant therapeutic benefit, especially if exercise is continued over time. When prescribing exercise either alone or as an adjunct to medication and psychotherapy, the complexity and the individual circumstances of each patient must be considered. When prescribing an exercise prescription, several caveats apply:

- Anticipate barriers - hopelessness and fatigue can make physical exertion difficult.
- Keep expectations realistic - some patients are vulnerable to guilt and self-blame if they fail to carry out the regime.
- Introduce a feasible plan - walking, alone or in a group, is often a good option.
- Accentuate pleasurable aspects - the specific choice of exercise should be guided by the patient's preferences, and must be pleasurable.
- A goal of 30 minutes of moderate-intensity aerobic exercise, three to five days a week is recommended for otherwise healthy adults (17.5 kcal/kg/week of total energy expenditure).
- Encourage adherence - greater antidepressant effects are seen when training continues beyond 16 weeks.

Evidence supporting this recommendation is of classes: A, C, R

Discuss Treatment Options

When considering treatment options, the primary goal is to achieve remission or to get the patient to be virtually symptom free (i.e., a PHQ-9 score of less than or equal to four or a HAM-D score of less than seven).

Psychotherapy versus Pharmacotherapy

Pharmacologic and/or psychotherapy interventions are effective in treating depression. Factors to consider in making treatment recommendations are symptom severity, presence of psychosocial stressors, presence of comorbid conditions, and patient preferences. If the presenting symptoms of depression are severe, the initial recommendation is to treat with antidepressants and psychotherapy. If the initial presentation is mild to moderate, either an antidepressant or psychotherapy (or both) is indicated. It is useful to also take into consideration cultural beliefs and sufficiency of (or lack of) resources such as transportation, finances and child care when making a decision whether to treat with medication and/or psychotherapy.

Depression treatment should take health beliefs into account. Patients who perceive more self-control of their health experience greater reduction in depressive symptoms, whether treated with psychotherapy or an antidepressant. Therefore, it is important to adequately assess a patient's expectations and beliefs in the controllability of depressive symptoms and functioning in order to treat major depression effectively and to minimize the risk of relapse and recurrence.

Psychotherapy

- Psychotherapy, especially focused psychotherapy, can significantly reduce symptoms, restore psychosocial and occupational functioning, and prevent relapse in patients with major depression
- Offer a referral for psychotherapy whenever psychological or psychosocial issues are prominent, or if the patient requests it. Individuals perceiving more self-control of their health experience greater depressive symptom reduction.
- Support and education in the primary care setting are critical and contribute to the likelihood of good follow through on treatment. It may help patients understand their options and resources if the primary care clinic explains that this is not the same as a course of psychotherapy.
- Maintenance psychotherapy is useful in managing chronic forms of major depressive disorder.
- Because both antidepressants and psychotherapy are effective, careful consideration to patient preference for mode of treatment is appropriate.

Evidence supporting this recommendation is of classes: A, C, M

Medications

For antidepressant medications, adherence to a therapeutic dose and meeting clinical goals are more important than the specific drug selected. The educational messages in Appendix A, (Treatment and Education box) in the original guideline document, may increase adherence.

Successful treatment often involves dosage adjustments and/or trial of a different medication at some point, to maximize response and minimize side effects. When antidepressant therapy is prescribed, the following key messages should be highlighted to support medication adherence and completion:

- Side effects from medication often precede therapeutic benefit and typically recede over time. It is important to expect some discomfort prior to the benefit.
- Successful treatment often involves dosage adjustments and/or trial of a different medication at some point, to maximize response and minimize side effects.
- Most people need to be on medication at least 6 to 12 months after adequate response to symptoms.
- Patients may show improvement at two weeks but need a longer length of time to really see response and remission.
- Take the medication as prescribed, even after one feels better. Premature discontinuation of antidepressant treatment has been associated with a 77% increase in the risk of relapse/recurrence of symptoms. On average, 50% to 85% of patients with a single episode of major depressive disorder will have at least one or more episode within 15 years of their first diagnosis. The probability of recurrence of depressive symptoms was found to be 25% after one year, 42% after

two years, and 60% after five years in one study. Each episode of recurrence increased the risk of subsequent episodes by 16%.

- Do not stop taking the medication without calling your provider. Side effects can be managed by changes in the dosage or dosage schedule.

Patient adherence is critical. In addition to medication monitoring, clinical management of patients placed on antidepressants should include the physician's support and reassurance.

Health care providers should carefully evaluate their patient in whom depression persistently worsens, or emergent suicidality is severe, abrupt in onset, or was not part of the presenting symptoms to determine what intervention, including discontinuing or modifying the current drug therapy, is indicated.

The provider should instruct the patient and the patient's caregiver to be alert for the emergence of agitation, irritability, and the other symptoms. The emergence of suicidality and worsening depression should be closely monitored and reported immediately to the health care provider.

Evidence supporting this recommendation is of classes: B, R

Selection of an Antidepressant Medication

Antidepressant drug selection should be based on:

- The patient's history of response to previous antidepressant medications (if any)
- The patient's comorbid psychiatric or medical conditions
- Clinician familiarity with specific antidepressants

Another resource for medication selection is the Texas Medication Algorithms which can be found at <http://www.dshs.state.tx.us/mhprograms/disclaimer.shtm>.

There is no evidence regarding choice of brand versus generic based on adverse clinical outcomes.

Refer to the original guideline document for information regarding pharmaceutical and therapeutic equivalents.

Evidence supporting this recommendation is of class: R

Consider discussing with the patient the specific side effect profiles, costs, and benefits of different antidepressants, including generics. Cost implications for patients need to be discussed between provider and patient.

1. Selective Serotonin Reuptake Inhibitor (SSRI); venlafaxine, duloxetine, mirtazapine, and bupropion

SSRIs, venlafaxine, duloxetine, mirtazapine and bupropion are frequently chosen as first-line therapy because of simplicity, side effect profiles, and community standards.

They generally lack the common adverse reactions (anticholinergic, sedative effects) of the tricyclics and cause fewer problems when taken in overdose. However, they may cause headache, nervousness, insomnia, and sexual side effects and may be more expensive as many may not yet be available as generics. Care must be taken to remain with either the brand name product or the same general product.

2. Secondary Amine Tricyclics

The literature clearly supports the effectiveness of tricyclics. Because of associated side effects, they are used less frequently as first-line agents.

Secondary amine tricyclics cause less orthostatic hypotension and sedation than tertiary amine tricyclics.

These medications should be monitored cautiously in patients with heart problems, or in patients with potential for drug interactions. Monitoring blood levels and electrocardiogram (EKG) may be advised.

3. Monoamine Oxidase Inhibitor (MAOI)

MAOIs, in general, should be restricted for patients who do not respond to other treatments because of their potential for serious side effects and the necessity of dietary restrictions. Patients with major depressive disorders with atypical features are one group for whom several studies suggest MAOIs may be particularly effective. However, in clinical practice, many psychiatrists start with SSRIs in such patients because of the more favorable adverse effect profile.

Medication interactions with antidepressant agents: Many antidepressant agents have clinically significant drug interactions, particularly those agents which undergo cytochrome P450 enzymatic metabolism in the liver. A complete discussion of this topic is beyond the scope of this guideline. Practitioners are advised to consult references such as the Physician's Desk Reference, American Hospital Formulary Service, Epocrates, or Micromedex for more information about drug interactions with specific agents, and to assess the significance of the interaction prior to prescribing antidepressants.

Elderly patients: Because of the potential for decreased renal and hepatic function, concomitant diseases and medications, the elderly are at higher risk of significant side effects or drug interactions with antidepressant medications. For elderly patients with moderate to severe depression, tricyclic antidepressants (TCAs) such as nortriptyline continue to be regarded as the most effective treatment. Consider starting at the lowest possible dose and increasing slowly to effective dose or until side effects appear. Tertiary amine tricyclics should generally be avoided in elderly patients because of the high

incidence of orthostatic hypotension, sedation, cognitive problems, and cardiac effects with these agents.

Evidence supporting this recommendation is of classes: A, C

Pregnancy: Approximately 5% to 14% of women experience significant mood or anxiety symptoms during pregnancy. Physicians must help patients weigh the risk of prenatal exposure to psychotropic medications against the risks of untreated psychiatric illness. The first line of treatment for mild to moderate depression includes increased instrumental support, which includes household tasks, childcare, etc., as well as interpersonal psychotherapy. When these non-medication options have failed or if patients have severe major depression or other Axis I (clinical disorders, other conditions that may be a focus of clinical attention) diagnoses, then the risks of untreated illness may outweigh the potential detrimental effects of certain antidepressant medications.

Risks of untreated maternal depression during pregnancy include:

- Preterm labor through increases in hormones
- Preeclampsia – one study found depression was associated with a 2.5-fold increased risk
- Increased risk of spontaneous abortion due to imbalance of nervous and endocrine systems

Maternal depression and impact on children:

- Parental depression is among the most consistent and well-replicated risk factors for depression, anxiety and disruptive disorders in children. The best data thus far comes from the STAR*D Child Report, where untreated depressed mothers showed an 8% increase of psychiatric diagnoses in their children ages 7 to 17 years versus an 11% reduction in rates of psychiatric diagnoses when mothers were treated and reached remission. There was no improvement at all before mothers responded to treatment (response equals 50% reduction in symptoms) and more improvement as a mother reached remission. This highlights another important reason to treat depressed mothers and to treat remission.

Patients commonly underestimate the risks of untreated maternal psychiatric illness while over emphasizing the risks of their psychotropic medications. Misperception about risk can lead both physicians and patients to terminate otherwise wanted pregnancies or avoid needed pharmacotherapy. By informing patients about the nature and magnitude of medication risks as well the risks of untreated illness, providers can help patients reach their own decisions. The clinician's goal is to provide a thorough risk-benefit assessment in order to minimize the risks of both depression and its treatment to the mother and child.

U.S. Food and Drug Administration (FDA) Pregnancy Risk Categories: (A) Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus. No currently available

antidepressant medication is rated A. (B) No evidence of risk in humans. Either animal findings show risk, but human findings do not; or if no adequate human studies have been done, animal findings are negative. Bupropion and maprotiline are rated B. (C) Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking. However, potential benefits may justify the potential risks. Amitriptyline, amoxapine, protriptyline, sertraline, trazodone, trimipramine, venlafaxine are rated C. (D) Positive evidence of risk. Investigational or post-marketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risks. If needed in a life-threatening situation or a serious disease, the drug may be acceptable if safer drugs cannot be used or are ineffective. Imipramine and nortriptyline are rated D. (X) Contraindicated in pregnancy. Studies in animals or human, or investigational or postmarketing reports have shown fetal risk which clearly outweighs any possible benefit to the patient. None of the currently available antidepressant medications are rated X.

The most reproductive safety information is available for the tricyclic antidepressants (TCAs) and SSRIs. Among the available pregnancy data, there is no evidence that these medications are associated with an increased risk of major congenital malformations. This is also true for sertraline, paroxetine, fluvoxamine, venlafaxine, and bupropion; however, there are fewer documented pregnancies with these medications.

In 2006 the FDA issued a warning for paroxetine due to an increased risk for cardiovascular malformations, primarily ventricular and atrial septal defects, compared to other antidepressants. Only first-trimester exposure to paroxetine at doses greater than 25 mg a day was associated with a greater risk of cardiac malformations in one study. Daily doses lower than 25 mg of paroxetine were not found to have an increased risk of any malformations in this study. Women of child-bearing age on paroxetine should be advised of the potential risk and other treatment options should be considered. The risk to infants exposed to paroxetine ranged from 1.5% to 2% compared to 1% in control groups.

There have been many case reports of perinatal syndromes with TCAs (e.g., jitteriness, irritability, bowel obstruction, urinary retention) as well as different SSRIs. Other studies have found an association between prenatal SSRI exposure and preterm delivery. In general, however, these reports have been limited to case reports and small series. In effect, some neonates in these reports may be exhibiting symptoms due to SSRI toxicity or withdrawal at birth, or alternatively, be more irritable and difficult to settle due to maternal depression and anxiety. To avoid perinatal withdrawal syndromes, some support slowly tapering antidepressants in the weeks prior to delivery. This is a debated treatment strategy since it also theoretically withdraws antidepressants just as women are entering the postpartum period, a time of increased risk for mood or anxiety symptoms. There is currently no clear evidence to suggest that reducing or discontinuing antidepressants in late pregnancy will reduce adverse neonatal effects.

Persistent pulmonary hypertension (PPHN) was not found to be a risk of SSRIs or non-SSRIs by mothers prior to the 20th week of gestation. However, use of SSRIs in late pregnancy may increase the risk of PPHN. The absolute

risk of developing PPHN is relatively small (6 to 12/1,000). Further studies are needed to evaluate the true risk of this potential complication.

Exposure to SSRIs in pregnancy may be associated with adverse neonatal effects. However, these are predominantly mild and short lived. Discontinuing antidepressants in women with a history of recurrent or severe depression is also associated with potentially adverse outcomes for both the mother and infant. Women with a history of depression who are planning to become pregnant should carefully consider the choice and timing of an antidepressant. It is recommended that throughout the pregnancy if a medication is continued, the minimum effective dose of an antidepressant needed to get remission should be used with ongoing maternal monitoring. The decision to continue treatment during the pregnancy should balance the risks and benefits to the mother and child and should be made on case-by-case basis.

Evidence supporting this recommendation is of classes: A, B, C, D, R

Lactation: Current knowledge on the use of antidepressants during lactation is insufficient. No randomized controlled trials have been completed due to ethical concerns. Existing knowledge is based on case reports, case series and pharmacokinetic studies. Adverse events may be more likely to be reported than non-effects.

Antidepressants may appear in breast milk in low concentrations. Because of the long half-life of these drugs and their metabolites, nursing infants may have measurable amounts in their plasma and tissues, such as the brain. This is particularly important during the first few months of life, with immature hepatic and renal function. Because these drugs affect neurotransmitter function in the developing central nervous system, it may not be possible to predict long-term neurodevelopmental effects. Use only when clearly needed and potential benefits outweigh the risks to the nursing infant. (Adapted from American Academy of Pediatrics (AAP) Policy Statement, Transfer of Drugs and Other Chemicals Into Human Milk, Pediatrics 2001; 108: 776-789). Breast-feeding offers several advantages: a) Breast-fed infants have lower rates of gastrointestinal disease, anemia, respiratory ailments, and otitis media compared to formula-fed infants; b) Nursing provides a unique opportunity for maternal-infant bonding. At the same time, the postpartum period (first 3 months following childbirth) is a particularly vulnerable period for psychiatric illness in women. Issues to be addressed when assessing the risks and benefits of psychotropic drug use during breast-feeding include the documented benefits of nursing, the potential adverse impact of untreated maternal mental illness on infant attachment and cognitive and behavioral development, and the effects of untreated mental illness on the mother.

Depression in the postpartum period can be disabling. Trials of cognitive behavioral therapy or interpersonal therapy, while safe, may not be effective—resulting in the need for antidepressant trials and/or electroconvulsive therapy (ECT). The use of antidepressants by nursing mothers is often acceptable as long as the mother-infant pair is monitored for the emergence of adverse effects or complications. Tricyclic antidepressants appear to be safe. However, there was one case report of respiratory distress in an infant of a mother treated with doxepin suggesting that this antidepressant should

be avoided during lactation. Data on the SSRIs suggest that sertraline and paroxetine are safe to use in nursing mothers suffering from depression.

There have been isolated case reports of infant toxicity in nursing mothers taking either doxepin or fluoxetine; however, studies have not revealed a consistent association between infant toxicity and any specific TCAs or SSRIs. The lack of adverse effects in 180 infants exposed to fluoxetine justifies its use especially if prescribed during the pregnancy or if there is a preferential history of response to this medication. Data on citalopram, fluvoxamine, bupropion and venlafaxine are more limited and their use cannot be recommended during breast-feeding at this time. Based on multiple case series, some researchers have recommended that the SSRI sertraline be considered the first-line treatment for nursing mothers with depression; however, sertraline may also carry risk in some mothers as demonstrated in one case report of an excessively high infant sertraline level in one mother-infant pair. Among the TCAs, nortriptyline has been the most studied treatment for nursing mothers, and no evidence of infant toxicity has been reported. Few studies have been done to evaluate the long-term consequences in children following antidepressant exposure through breast milk. One study followed children whose mothers nursed while taking TCAs. At preschool age these children were developmentally similar to non-exposed children. There have been no similar studies following children whose mother nursed while taking SSRIs.

Evidence supporting this recommendation is of classes: C, R

Refer to Table 1 in the original guideline document for dosage recommendations, safety, and side effects of antidepressants.

For up-to-date prescribing information, the following drug references may be used:

- The Physician's Desk Reference: <http://www.pdr.net>
- The American Hospital Formulary Service (AHFS): <http://ashp.org/ahfs>
- Micromedex: <http://www.micromedex.com>
- Epocrates: <http://epocrates.com>

Herbals and Dietary Supplements

Caution: many drugs interact with St. John's wort, including other antidepressants, warfarin, oral contraceptives, antiretroviral, anti-cancer and anti-rejection drugs. Care should be taken to ask all patients what medications they are taking, including over-the-counter and supplements, to avoid these interactions.

Hypericum perforatum (St. John's wort) is popularly thought to be an herbal remedy for depression. The Hypericum Depression Trial Study Group concluded that the data does not support the use of Hypericum perforatum instead of antidepressants or psychotherapy. It has no proven efficacy in standard clinical care of patients with major depression.

SAM-e (S-adenosyl methionine). S-Adenosyl - L-methionine (SAM-e) is a natural compound that has been studied as a treatment option for depression. As of 2002, there were 11 controlled against placebo studies, 14 controlled against tricyclic antidepressant studies, and 2 meta-analyses. Essentially these studies show that SAM-e is superior to placebo and comparable to tricyclics in the treatment of outpatients with major depression. Effective oral doses seem to be in the 400 to 1,600 mg a day range as compared to doses of 400 mg a day of tricyclics. Side effects are less common than with tricyclics (7% with oral and intramuscular SAM-e versus 28% with oral tricyclic) and include mild insomnia, lack of appetite, constipation, nausea, dry mouth, diaphoresis, dizziness, and nervousness. Increased anxiety and hypomania have been reported in patients with bipolar depression. Interactions with other medications have not been studied and are unknown. Comparisons to newer antidepressants have not yet been done.

Other herbal remedies and dietary supplements, such as kava-kava, Omega-3 fatty acid, (docosahexaenoic acid) and valerian root, have not been proven effective for the treatment of depression and may or may not be safe.

Herbal products and nutritional supplements are not evaluated or regulated by the U.S. Food and Drug Administration for safety, efficacy or bioavailability.

Evidence supporting this recommendation is of classes: A, M, R

Establish Follow-Up Plan

Proactive follow-up contacts (in person, telephone) based on the Collaborative Care Model has been shown to significantly lower depression severity.

If the primary care provider is seeing some improvement, continue working with that patient to augment or increase medication dosage to reach remission. This can take up to three months. Don't give up on the patient whether treating in primary care or referring. Stay connected through consultation or collaboration and take the steps needed to get the patient to remission. This can take longer and can take several medication interventions or other steps. The STAR*D studies have shown that primary care can be just as successful as specialty care.

Establish and maintain initial follow-up contact intervals (office, phone, other).

One study found that improving attitudes towards antidepressant medications along with the patient's ability to handle medication side effects are key factors in promoting greater adherence to maintenance treatment and thus greater likelihood of preventing relapse.

Interventions toward depression improvement may include patient follow-up through phone calls, visits or other contacts. Interventions are critical to educating the patient regarding the importance of preventing relapse, safety and efficacy of medications and management of potential side effects.

If symptoms are severe: Weekly contacts may be needed until significant response is achieved. Response is defined as a significant level of improvement; or clinically relevant reduction of more than 50% on a severity scale such as PHQ-9 or the Hamilton Rating Scale for Depression.

If mild or moderate symptoms are present: Contact should be every two to four weeks.

This protocol should be in place until remission or best possible response is achieved; treatment should be then spaced out as clinically warranted.

For maintenance medication: Contacts can occur every 3 to 12 months if everything else is stable.

When considering how long to continue medication after the remission of acute symptoms, two issues need to be considered: maintenance and prophylactic treatment.

Patients who require several medication changes to achieve remission of an acute major depressive episode have a higher rate of relapse and a shorter period of time until relapse in comparison to patients who require fewer medication changes to achieve remission.

Some evidence suggests treatment be continued through a two episode cycle for a period of years. See also Annotation #13: "Evaluate Dose, Duration, Type and Adherence with Medication and/or Psychotherapy. Reconsider Accuracy of Diagnosis or Impact of Comorbidities" and Annotation #15, "Continuation and Maintenance Treatment for 6-12 Months."

There are significant data to support the efficacy of antidepressants in preventing the recurrence of a major depressive episode. Although more research needs to be conducted, current findings indicate that patients who are at highest risk of future episodes have had multiple prior episodes or were older at the time of the initial episode. These patients are candidates for long-term or lifetime prophylactic treatment.

Lifetime treatment may be indicated for patients:

- Aged greater than 60 at first episode
- Aged greater than 40 with more than two episodes
- With greater than three episodes

The adjunctive use of targeted psychotherapy may be considered in some patients, both during acute phase treatment as well as during long-term maintenance. Please refer to section discussing role of psychotherapy.

The decision to consider prophylactic treatment is also influenced by multiple factors:

- The severity of the depressive episode
- The frequency of past depressions

- The risk of suicide
- The risk of potential adverse medication effects

If discontinuation of treatment is thought to be appropriate or necessary despite the known risks, a plan of action should be in place for prompt intervention if relapse occurs.

Evidence supporting this recommendation is of classes: A, M, R

Referral

Consider involvement of a behavioral health care provider for the following:

- Patient request for psychotherapy
- Presence of severe symptoms and impairment in patient
- Diagnostic question
- Presence of other psychiatric condition (e.g., personality disorder, history of mania)
- Substance abuse questions
- Clinician discomfort with the case
- Initial treatment does not result in a successful outcome
- Patient request for more specialized treatment

12. Is Patient Responding Adequately?

The goal of treatment should be to achieve remission. Remission is defined as the absence of depressive symptoms, or the presence of minimal depressive symptoms. Response is defined as a 50% or greater reduction in symptoms (as measured on a standardized rating scale) and partial response is defined as a 25% to 50% reduction in symptoms. There are different definitions of these issues in the literature, and the time at which one measures is also debated. Studies measure for effectiveness at 4, 8, and 12 weeks. Frequently, the level of response at 4 weeks is predictive of response at 8 or 12 weeks. Remission rates from research-based, 8-week randomized placebo-controlled efficacy trials using medications with depressed, symptomatic volunteers range from 25% to 40%.

If primary care provider is seeing some improvement, continue working with that patient to augment or increase dosage to reach remission. This can take up to three months.

A reasonable criterion for extending the initial treatment is if the patient is experiencing a 25% or greater reduction in baseline symptom severity at 4 weeks of therapeutic dose. If the patient's symptoms are reduced by 25% or more, but the patient is not yet at remission, and if medication has been well tolerated, continue to prescribe. Raising the dose is recommended. Improvement with psychotherapy is often a bit slower than with pharmacotherapy. A decision regarding progress with psychotherapy and the need to change or augment this type of treatment may require 8 to 10 weeks before evaluation.

Evidence supporting this recommendation is of classes: A, D, M, R

13. Evaluate Dose, Duration, Type and Adherence With Medication and/or Psychotherapy. Reconsider Accuracy of Diagnosis or Impact of Comorbidities

Key Points:

- The key objectives of treatment are:
 - Acute phase goal for treatment of major depression is remission of symptoms. Remission may be expected in up to 40% of patients with single treatment. Remaining patients will need to be reevaluated for reasons for lack of remission and decisions made about next steps. Evidence shows that for these patients, at best, 40% will not be able to achieve remission. For those patients, the goal is to reduce symptoms to manageable levels.
 - Reduction of relapse and recurrence of major depression.
 - Return to previous level of occupational and psychosocial function.

Evidence supporting this recommendation is of classes: R

Treatment Considerations

People of differing racial/ethnic groups can be successfully treated using currently available evidence-based interventions when differential personal elements, from biological to environmental to cultural, are considered during the treatment planning process.

Evidence supporting this recommendation is of class: R

Psychotherapy

A switch from antidepressant to psychotherapy or vice versa appears useful for nonresponders to initial treatment.

Psychotherapy may provide better outcomes on adjustment/functional measures such as mood, suicidal ideation, work and interests; medication treatment may be superior on vegetative symptoms such as sleep and appetite.

There are numerous types of psychotherapy, just as there are numerous types of medication. If a patient has received psychotherapy and not responded, evaluate the treatment he/she received and consider another type. Cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), short-term psychodynamic psychotherapy (STPP) and problem-solving treatment (PST) have documented efficacy. In mild to moderate levels of depression, psychotherapy can be equally as effective as medication. With severe depression, antidepressant medication may be more helpful in the acute

phases. There is documentation to support lower relapse rates among patients receiving psychotherapy.

Evidence supporting this recommendation is of classes: C, M, R

Pharmacologic Therapy

- If there is less than 25% reduction of symptoms after six weeks at therapeutic dose (i.e., partial positive response to medication), add or substitute another treatment modality.
- When considering how long to continue medication after remission of acute symptoms, two issues need to be considered: continuation and maintenance treatment.

The best candidates for maintenance therapy are patients who have had two previous episodes of major depression, or who have had two episodes of major depression but have also had rapid recurrence of episodes, or are older in age at the onset of major depression (more than 60 years of age), have had severe episodes of major depression or a family history of a mood disorder. Maintenance therapy should also be considered for at risk patients with double depression, patients with comorbid anxiety disorder, or substance abuse. Patients whose major depression has a seasonal pattern are also at risk for recurrence.

It is suggested that the dose of antidepressant medication that leads to satisfactory acute therapeutic response should be maintained during long-term treatment to prevent relapse and recurrence of depression.

All patients experiencing major depression should be withdrawn gradually from antidepressants. Patients experiencing the first episode of major depression should continue medication treatment for six to twelve months (including acute and continuation therapy). Patients undergoing medication treatment for the second episode of major depression should continue medication treatment for three years. Patients who have three or more episodes of major depression or who have two episodes with complicating factors (such as rapid recurrence of episodes, more than 60 years at age of onset of major depression, severe episodes or family history), should continue medication treatment indefinitely.

Premature treatment discontinuation can be triggered by a number of factors including lack of adequate education about the disease, failure on the part of either physician or the patient to establish goals for follow-up, psychosocial factors and adverse side effects. Early drug discontinuation contributes to probability of relapse and recurrence.

Evidence supporting this recommendation is of classes: A, C, D, R

See also "Establish Follow-Up Plan and Treatment Plan" section in Annotation #11: "Treatment Plan" and Annotation #15: "Continuation and Maintenance Treatment for 6-12 Months."

14. Consider Other Strategies

Key Points:

- When identifying that a patient is treatment resistant, the first steps are to reassess the diagnosis, look for comorbid medical and psychiatric problems that might be interfering with recovery, and to review the adequacy and adherence to previous treatment. For purposes of making recommendations for primary care providers, the guideline developers define true treatment resistance as failure to achieve remission with an adequate trial of therapy and three different classes of antidepressants at adequate duration and dosage.
- Augmentation strategies may be used for partial responders and combinations of antidepressants (when each has a different mechanism) have been shown to be options in those who fail to achieve remission.
- Partial or full hospitalization may be indicated in patients who have failed outpatient management, particularly if safety issues are a concern.
- Use of bright light therapy for treatment of major depression with a seasonal specifier is well established.
- Electroconvulsive treatment is very effective and can sometimes be administered safely in an outpatient setting.

If the patient is newly involved in psychotherapy, the following are important:

- Return visit in eight to ten weeks to evaluate progress
- Contact with patient in four to six weeks
- Communicate with therapist in four to six weeks
- Therapy can take eight to ten weeks to show improvement

If the patient has been treated with medication and there is less than a 25% reduction in symptoms when evaluated at four to six weeks, switch to a different medication. If there is a partial response and side effects are not prohibitive, increase the dose. As part of the evaluation, using a standardized assessment tool will serve as a documentation of progress.

If the above measures have not achieved remission when re-evaluated 4 to 6 weeks later, consider:

- Re-evaluating the diagnosis
- Switching to a different antidepressant medication. After a failed trial of citalopram, remission rates in the STAR*D studies were 21.3% for bupropion SR, 17.6% for sertraline, and 24.8% for venlafaxine XR.
- Augmentation strategies (such as lithium or low-dose thyroid)
- Other biological treatments (such as a second antidepressant)
- Adding a new medication
- Failure of a drug in one family does not rule out possible benefit from other drugs in that family. This is particularly true for SSRIs.
- Referral to psychiatry for possible MAOI, electroconvulsive therapy (ECT) treatment

- Looking for comorbidities, such as substance abuse issues and involving addiction specialists as needed
- Consider the possibility of a bipolar diathesis. Bipolar patients require a different treatment approach and may not consistently come forward with their hypomanic, mixed, or manic histories
- Referral to behavioral health if there are personality disorders present
- If only on medication, add psychotherapy
- Whether adequate engagement of patient/family is present and that recommendations are being followed (adherence)
- Obtaining a consultation or referral to behavioral health specialists

Evidence supporting this recommendation is of classes: A, B, D

Augmentation therapy is used for those situations where the patient's depression is either treatment-resistant or partially responsive to treatment. This is a good time to consult and/or refer to a behavioral health specialist.

Augmentation methods include:

- Lithium augmentation with TCAs. Lithium augmentation with SSRI (caution -- case reports of serotonin syndrome).

Evidence supporting this recommendation is of classes: A, D

- T₃ augmentation of TCA.

Evidence supporting this recommendation is of class: A, R

- Stimulant drugs augmentation of TCA/SSRI ("jump-start response").
- TCA-SSRI combination (caution -- elevated TCA level – to be monitored).

Evidence supporting this recommendation is of classes: C, D

- Bupropion -- SSRI combination.

Evidence supporting this recommendation is of class: A, D

- Mirtazapine -- SSRI combination.

Evidence supporting this recommendation is of classes: A, D

- Buspirone -- SSRI combination.

Evidence supporting this recommendation is of classes: C, D

- Carbamazepine/valproic acid -- TCA combination (caution - may decrease TCA level). Carbamazepine/valproic acid - SSRI combination

Evidence supporting this recommendation is of class: D

- Atypical antipsychotic -- antidepressant combination

Evidence supporting this recommendation is of class: D

Other Therapies

Based on work group consensus, the following therapies are in order of the likely clinical judgment and decision process of a primary care provider.

Hospitalization

Partial or full hospitalization may be indicated in patients who have failed outpatient management, particularly if safety issues are a concern.

Light Therapy

Use of bright light therapy for treatment of major depression with a seasonal specifier is well established. Additionally, there is preliminary evidence of the efficacy of bright light therapy for some other types of depressive symptom patterns, including non-seasonal depression and milder variations of seasonal depressive patterns. Bright light therapy may also quicken and enhance the effects of antidepressant medication. Preliminary evidence suggests efficacy in special populations such as moderately mentally retarded people and pregnant women. This is of significance because mentally retarded patients may be less likely to benefit from psychotherapy, and there are no antidepressants approved for use by pregnant women. A recent open study of light therapy for treatment of major depression during pregnancy yielded promising results, although further research is needed to clearly establish safety and efficacy during pregnancy. Although the light exposure dosage (typically 5,000 to 10,000 lux) and exposure length (typically 30 to 60 minutes) have been fairly standard for seasonal affective disorder treatment, research on bright light therapy for other types of depression has not necessarily utilized standard dosages and exposure times. Light therapy cannot be endorsed as an evidence-based treatment for antepartum and postpartum depressed women. It is important that any light therapy treatment utilize equipment that eliminates ultraviolet frequencies and produces bright light of known spectrum and intensity. For these reasons, use of client-constructed light therapy units is contraindicated.

Evidence supporting this recommendation is of classes: A, D, M, R

Electroconvulsive Treatment (ECT)

Electroconvulsive treatment is very effective and can sometimes be administered safely in an outpatient setting. ECT does not cure depression, and a successful ECT treatment should be followed by a plan to prevent relapse of the depression. A patient considering ECT would need to be able to tolerate anesthesia, and should consult with a psychiatrist about the risks and benefits.

Factors that may suggest a given patient may be an ECT candidate include:

- Geriatric depression
- Antidepressant medications have not been tolerated or pose a significant medical risk
- Antidepressant medication trials have not been successful
- ECT has been successful in previous episodes
- Catatonia is present
- A rapid response is needed because of severe suicide risk or because the patient's health has been significantly compromised by the depression (i.e., severe cachexia, inability to attend to the activities of everyday living)
- Depression with psychotic features
- Melancholic symptoms are predominant
- Depression and Parkinsonism

Evidence supporting this recommendation is of classes: A, M, R

For more information about ECT, see the "Resources Available" table in the "Support for Implementation" section of the original guideline document.

Vagus Nerve Stimulation (VNS)

VNS involves the use of an implantable device, which provides intermittent stimulation to the left vagus nerve (80% afferent to the central nervous system). It is used as an adjunctive treatment along with other modalities such as use of psychotropic medications. It has only been studied in refractory or treatment resistant depression.

Side effects include voice alterations (generally just while one is receiving the 30 seconds of stimulation each 5 minutes), increased rate of neck pain, cough, dyspnea, and dysphagia. At this point in time, VNS is approved by the FDA for treatment of resistant depression. However, given the lack of double blind controlled studies and the somewhat disappointing result in the one available, this does not meet the threshold for category A evidenced-based at this point in time. But a promising new therapy remains to be fully proven.

Evidence supporting this recommendation is of class: A, D

Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that stimulates the brain in vivo using high intensity, pulsed electron-magnetic fields. Recent research has examined the use of rTMS in the treatment of major depressive disorder. In the procedure, a hand-held stimulating coil is applied directly to the patient's head and delivers a magnetic pulse to the cortex. Results of research studies to date have been inconsistent and inconclusive.

The FDA has not yet approved rTMS for general clinic use, and it must be considered, at this time, investigational.

Evidence supporting this recommendation is of class: A, C, M

Magnetic Seizure Therapy (MST)

Magnetic seizure therapy uses focused stimulation (generally of the right frontal area) to induce a focal seizure. This is designed to obtain efficacy of ECT without the cognitive side effects (which generally occur when seizures spread to the hippocampus). One open label trial showed less amnesia and faster reorientation than ECT and some improvement in depression scores.

At this time, MST holds research promise but is not yet evidence-based.

Evidence supporting this recommendation is of class: R

Deep Brain Stimulation (DBS)

Deep brain stimulation is the process of implanting an electrode to stimulate the subgenual cingulate gyrus with high-frequency impulses to diminish depression in treatment refractory patients with major clinical depression. One open label trial showed four out of six patients achieved remission after surgery (and those with sham sessions did not). At two months, five out of six patients were in remission and four out of six were in remission at six months.

At this time, DBS is an interesting and promising research approach but cannot be considered evidence-based.

Evidence supporting this recommendation is of class: D

Acupuncture

Although acupuncture is known to be an alternative therapy for the treatment of depression, it has shown mixed results. Acupuncture may be an alternative for those who reject traditional treatments, for those who do not show adequate response to traditional treatments or for those in whom antidepressants may be contraindicated (frail, elderly or pregnant women). Electro-acupuncture may be a treatment of choice for those who are unable to comply with classic tricyclic antidepressants because of their anticholinergic side effects. It is felt that additional larger controlled and longitudinal studies need to be done for endorsement as a recommended treatment for depression.

Evidence supporting this recommendation is of classes: A, R

15. Continuation and Maintenance Treatment for 6-12 Months

Acute treatment (usually the first three months of treatment) refers to treating with antidepressant medication in order to achieve remission of major depressive symptoms. Remission is defined as having minimal residual symptoms (Hamilton Rating Scale for Depression score less than 7 or PHQ-9 score of 4 or less). Continuation therapy is the phase where one continues

to treat with antidepressants in order to keep the patient free of symptoms for the duration of the current episode. By definition this is considered to be at least 6 months long, but lately the evidence supports a 6 to 12 months duration. However, consider in elderly populations it may take longer to respond to acute treatment. Therefore, the maintenance period of treatment may need to be extended. Maintenance therapy is designed to prevent recurrence of new or future episodes of major depression.

Complicating factors are those situations where evidence either shows or suggests higher rates of recurrence after stopping antidepressants and include:

- Pre-existing dysthymia
- Inability to achieve remission
- Recurrence of symptoms in response to previously attempted lowering dose or discontinuation

With the wide array of half-lives and therapeutic dose ranges for the various existing antidepressants, it is beyond the scope of this guideline to discuss detailed discontinuation strategies.

When feasible (e.g., the starting dose is not the same as therapeutic doses), it is recommended that the dose be tapered over a period of weeks to several months when discontinuing an antidepressant.

See also "Establish Follow-Up Plan and Treatment Plan" in Annotation #11 and Annotation #13: "Evaluate Dose, Duration, Type and Adherence with Medication and/or Psychotherapy. Reconsider Accuracy of Diagnosis and Impact of Comorbidities."

Evidence supporting this recommendation is of classes: A, B, C, M, R

Definitions:

Evidence Grading System

A. Primary Reports of New Data Collection

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test

- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

A detailed and annotated clinical algorithm is provided for [Major Depression in Adults in Primary Care](#).

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Improved diagnosis of primary care patients with major depression
- Effective treatment/management of patients with major depression
- Reduced relapse and recurrence of major depression

POTENTIAL HARMS

Side Effects of Anti-depressant Medication

- Selective serotonin re-uptake inhibitors (SSRIs), venlafaxine, duloxetine, mirtazapine and bupropion may cause headache, nervousness, insomnia, and sexual side effects and may be more expensive as some are not yet available as generics. Care must be taken to remain with either brand name product or the same generic product.
- Secondary amine tricyclics are used less frequently as first-line therapy because of associated side effects. These medications should be monitored cautiously in patients with heart problems, or in patients with potential for drug interactions. Monitoring blood levels and electrocardiogram may be advised.
- Monoamine oxidase inhibitors (MAOIs) should be restricted for patients who do not respond to other treatments because of their potential for serious side effects and the necessity of dietary restrictions.
- Lithium augmentation with selective serotonin reuptake inhibitors poses the risk of serotonin syndrome.
- Many antidepressant agents have clinically significant drug interactions, particularly those agents which undergo cytochrome P450 enzymatic metabolism in the liver.
- Tricyclic antidepressant (TCA)-SSRI combination should be given with caution as it increases TCA levels
- Stimulant drugs augmentation of TCA-SSRI: cases of sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant medication at usual doses for attention-deficit hyperactivity disorder (ADHD). Adults with serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease or other serious cardiac problems should not be treated with stimulant medications.
- Side effects of S-Adenosyl-L- methionine (SAM-e) include mild insomnia, lack of appetite, constipation, nausea, dry mouth, diaphoresis, dizziness, and nervousness. Increased anxiety and hypomania have been reported in patients with bipolar depression.

Subgroups Most Likely to Be Harmed

- Elderly patients: Because of the potential for decreased renal and hepatic function, concomitant diseases and medications, the elderly are at higher risk of significant side effects or drug interactions with antidepressant medications. Tertiary amine tricyclics should generally be avoided in elderly patients because of the high incidence of orthostatic hypotension, sedation, cognitive problems, and cardiac effects with these agents.
- Pregnant Women: There have been many case reports of perinatal syndromes with TCAs (e.g., jitteriness, irritability, bowel obstruction, urinary retention) as well as most SSRIs. Other studies have found an association between prenatal SSRI exposure and preterm delivery. In general, however, these reports have been limited to case reports and small series. Use of SSRIs in late pregnancy may increase the risk of persistent pulmonary hypertension (PPHN).

In 2006 the FDA recently issued a warning for paroxetine due to an increased risk for cardiovascular malformations, primarily ventricular and atrial septal defects, compared to other antidepressants. Only first-trimester exposure to

paroxetine at doses greater than 25 mg a day was associated with a greater risk of cardiac malformations in one study. Women of child-bearing age on paroxetine should be advised of the potential risk and other treatment options should be considered. The risk to infants exposed to paroxetine ranged from 1.5% to 2% compared to 1% in control groups.

- Nursing infants: Antidepressants may appear in breast milk in low concentrations. Because of the long half-life of these drugs and their metabolites, nursing infants may have measurable amounts in their plasma and tissues, such as the brain. Because these drugs affect neurotransmitter function in the developing central nervous system, it may not be possible to predict long-term neurodevelopmental effects. Use only when clearly needed and potential benefits outweigh the risks to the nursing infant. Sertraline may carry risk in some mothers as demonstrated in one case report of an excessively high infant sertraline level in one mother-infant pair. There was one case report of respiratory distress in an infant of a mother treated with doxepin, suggesting that this antidepressant should be avoided during lactation.

Refer to Table 1 in the original guideline document for more details on side effects of antidepressants.

CONTRAINDICATIONS

CONTRAINDICATIONS

Use of client-constructed light therapy units is contraindicated.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This clinical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. An action group is formed when a topic is selected as an initiative.

In addition to the action group goals and measures, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

Key Implementation Recommendations

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Detection and diagnosis
 - Systems in place to reliably determine if a patient is depressed
 - Use of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV TR) criteria and structured questionnaires (such as Patient Health Questionnaire-9 [PHQ-9])
2. Patient-centered care, education and self-management programs
 - Structured attention to patient preferences
 - Patient and family education materials/protocols
 - Patient self-management skills such as journal writing or self-monitoring
 - Involving families as well in care management programs
 - Care manager role to coordinate the disease management for patients with depression including such things as patient contacts, education, self-management tools and tips.
3. Mental health/behavioral medicine specialist involvement
 - Shared care – collaborative care between behavioral health specialists and primary care providers in the primary care setting. Care manager and/or primary care provider consulting with psychiatry on a regular basis regarding the case load of patients with depression managed in the depression care management program.
 - Appointment availability – access to behavioral health in timely manner
4. Outcomes measurement
 - Build in plans for outcome measures as well as ongoing process measures
 - Response rate to various treatments
 - Remission rates – improvement in response is stable over time
5. Systems to coordinate care, ensure continuity and keep providers informed of status
 - Build automated processes for the first four core elements wherever possible

- Reduce dependence on human behavior to ensure delivery of patient care processes
- Use of components of the chronic care model for depression care, i.e., use of registries, community outreach, etc.
- Structured frequent monitoring and follow-up with patient
- Nurse/care manager phone care and use of other modalities for patient follow-up

IMPLEMENTATION TOOLS

Clinical Algorithm
Patient Resources
Pocket Guide/Reference Cards
Quality Measures

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

RELATED NQMC MEASURES

- [Major depression in adults in primary care: percentage of patients with a new diagnosis of major depression, with documentation of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision \(DSM-IV TR\) criteria within the three months prior to initial diagnosis.](#)
- [Major depression in adults in primary care: percentage of patients who have a depression follow-up contact within three months of initiating treatment.](#)
- [Major depression in adults in primary care: percentage of patients whose symptoms are reassessed by the use of a quantitative symptom assessment tool \(such as Patient Health Questionnaire \[PHQ-9\]\) within three months of initiating treatment.](#)
- [Major depression in adults in primary care: percentage of patients whose results on 2 quantitative symptom assessment tools \(such as Patient Health Questionnaire \[PHQ-9\]\) decrease by 50 percent within three to seven months after diagnosis.](#)
- [Major depression in adults in primary care: percentage of patients whose results on 2 Patient Health Questionnaires \(PHQ-9s\) score less than 5 or similar testing \(Hamilton Rating Scale for Depression score of 7 or less\) within three to seven months after diagnosis.](#)
- [Major depression in adults in primary care: percentage of patients with diabetes with documentation of screening for depression.](#)

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Major depression in adults in primary care. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2007 May. 87 p. [239 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 Jan (revised 2007 May)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

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GUIDELINE COMMITTEE

Committee on Evidence-Based Medicine

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Michael Trangle, MD is a consultant for Interactive Forums, consulting on best practices and doing focus group work.

No other work group members have potential conflicts of interest to disclose.

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GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Major depression in adults in primary care. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 May. 81 p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the [Institute for Clinical Systems Improvement \(ICSI\) Web site](#).

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Major depression in adults in primary care. Executive summary. Bloomington (MN): Institute for Clinical Systems Improvement, 2007 May. 2 p. Electronic copies: Available from the [Institute for Clinical Systems Improvement \(ICSI\) Web site](#).
- ICSI pocket guidelines. April 2006 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2006. 298 p.

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PATIENT RESOURCES

None available

NGC STATUS

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